<u>Remarks</u>

No new matter has been added. If there are any questions, please contact the undersigned by telephone.

Respectfully submitted,

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Attachment: Amendment
Amendment with Underscoring to indicated additional material

PYRAZOLOPYRIDINES

AND METHODS OF MAKING AND USING THE SAME

This non-provisional application is a continuation application of PCT/US2003/027722, filed on September 5, 2003, which is a continuation-in-part and claims benefit of priority of U.S. Provisional application 60/408,811, filed September 6, 2002. The entire disclosure of each of the aforementioned patent applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

TGFβ (Transforming Growth Factor β) is a member of a large family of dimeric polypeptide growth factors that includes activins, inhibins, bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and mullerian inhibiting substance (MIS). TGFβ exists in three isoforms (TGFβ1, TGFβ2, and TGFβ3) and is present in most cells, along with its receptors. Each isoform is expressed in both a tissue-specific and developmentally regulated fashion. Each TGFβ isoform is synthesized as a precursor protein that is cleaved intracellularly into a C-terminal region (latency associated peptide (LAP)) and an N-terminal region known as mature or active TGFβ. LAP is typically non-covalently associated with mature TGFβ prior to secretion from the cell. The LAP- TGFβ complex cannot bind to the TGFβ receptors and is not biologically active. TGFβ is generally released (and activated) from the complex by a variety of mechanisms including interaction with thrombospondin-1 or plasmin.

Following activation, TGFβ binds at high affinity to the type II receptor (TGFβRII), a constitutively active serine/threonine kinase. The ligand-bound type II receptor phosphorylates the TGFβ type I receptor (Alk 5) in a glycine/serine rich domain, which allows the type I receptor to recruit and phosphorylate downstream signaling molecules, Smad2 or Smad3. See, e.g., Huse, M. et al., *Mol. Cell.* 8: 671-682 (2001). Phosphorylated Smad2 or Smad3 can then complex with Smad4, and the entire hetero-Smad complex translocates to the nucleus and regulates transcription of various TGFβ-responsive genes. See, e.g., Massagué, J. *Ann. Rev. Biochem. Med.* 67: 773 (1998).

Activins are also members of the TGFβ superfamily which are distinct from TGFβ in that they are homo- or heterodimers of activin βa or βb. Activins signal in a similar manner to

TGFβ, that is, by binding to a constitutive serine-threonine receptor kinase, activin type II receptor (ActRIIB), and activating a type I serine-threonine receptor, Alk 4, to phosphorylate Smad2 or Smad3. The consequent formation of a hetero-Smad complex with Smad4 also results in the activin-induced regulation of gene transcription.

Indeed, TGFβ and related factors such as activin regulate a large array of cellular processes, e.g., cell cycle arrest in epithelial and hematopoietic cells, control of mesenchymal cell proliferation and differentiation, inflammatory cell recruitment, immunosuppression, wound healing, and extracellular matrix production. See, e.g., Massagué, J. *Ann. Rev .Cell. Biol.* 6: 594-641 (1990); Roberts, A. B. and Sporn M. B. *Peptide Growth Factors and Their Receptors,* 95: 419-472 Berlin: Springer-Verlag (1990); Roberts, A. B. and Sporn M. B. *Growth Factors* 8:1-9 (1993); and Alexandrow, M. G., Moses, H. L. *Cancer Res.* 55: 1452-1457 (1995). Hyperactivity of TGFβ signaling pathway underlies many human disorders (e.g., excess deposition of extracellular matrix, an abnormally high level of inflammatory responses, fibrotic disorders, and progressive cancers). Similarly, activin signaling and overexpression of activin is linked to pathological disorders that involve extracellular matrix accumulation and fibrosis (see, e.g., Matsuse, T. et al., *Am. J. Respir. Cell Mol. Biol.* 13: 17-24 (1995); Inoue, S. et al., *Biochem. Biophys. Res. Comm.* 205: 441-448 (1994); Matsuse, T. et al, *Am. J. Pathol.* 148: 707-713 (1996); De Bleser et al., *Hepatology* 26: 905-912 (1997); Pawlowski, J.E., et al., *J. Clin. Invest.* 100: 639-648 (1997); Sugiyama, M. et al., *Gastroenterology* 114: 550-558 (1998); Munz, B. et al., *EMBO J.* 18: 5205-5215 (1999)) and inflammatory responses (see, e.g., Rosendahl, A. et al., *Am. J. Repir. Cell Mol. Biol.* 25: 60-68 (2001)). Studies have shown that TGFβ and activin can act synergistically to induce extracellular matrix (see, e.g., Sugiyama, M. et al., *Gastroenterology* 114: 550-558, (1998)). It is therefore desirable to develop modulators (e.g., antagonists) to signaling pathway components of the TGFβ family to prevent/treat disorders related to the malfunctioning of this signaling pathway.